REMARKS

Applicant respectfully requests reconsideration. Claims 32-47 were previously pending in this application. Claims 48-53 were previously withdrawn. No claims are amended herein. No claims are cancelled. No new claims are added. As a result, claims 32-47 are pending for examination with claim 32 being an independent claim. No new matter has been added.

Double Patenting Rejection

Claims 32-47 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,635,624.

Applicants may file a Terminal Disclaimer depending on the claims that are found to be allowable. It is respectfully requested that the rejection be delayed until claims are found to be allowable.

Accordingly, withdrawal of the rejection of claims 32-47 is respectfully requested.

Rejection Under 35 U.S.C. 112

Claims 32-47 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method as claimed, wherein the vector comprises a gene encoding the hepatitis B virus (HBV) surface antigen protein, and further wherein the vector comprises a promoter operably linked to the gene, such that the antigen is expressed in the subject, does not reasonably provide enablement for the use of a vector encoding any HBV antigen. The Examiner essentially repeats arguments of record (Office Action dated October 23, 2006, pages 3-6) including an analysis of several Wands factors in support of a conclusion of lack of enablement and then addresses arguments presented by Applicants. Applicants maintain arguments of record (Response to Office Action dated February 23, 2007) and incorporate those arguments herein by reference in their entirety. Applicants also present a Wands analysis and address each new point raised by the Examiner.

As indicated above, the Examiner acknowledges that the application is enabled for a method as claimed, wherein the vector comprises a gene encoding the HBV surface antigen protein.

Furthermore, the Examiner asserts that the specification does not reasonably provide enablement for the use of a vector encoding any HBV antigen.

Applicants present a Wands analysis below that supports a scope of enablement of the HBV antigen genus as claimed. Factors to be considered when determining scope of enablement and whether any necessary experimentation is "undue" include, but are not limited to: breadth of the claims, nature of the invention, state of the prior art, level of one of ordinary skill, level of predictability in the art, amount of direction provided by the inventor, existence of working examples, and quantity of experimentation needed to make or use the invention based on the content of the disclosure.

With regard to the breadth of the claims, at issue is the breadth of the genus hepatitis B virus antigens. Antigen is an art known term that refers to a substance capable of inducing a specific immune response (*See* page 4, column 2, paragraph 2, *Cellular and Molecular Immunology*, Abbas AK, et al., Copyright 1991). Exemplary HBV antigens are disclosed in the specification and include HBV proteins and portions of proteins (i.e., fragments) such as HBV surface antigens and core antigens (*See*, for example, page 4, line 2; page 5, lines 16-17; and page 6 lines 10-15 of the instant specification). In the instant Office Action the Examiner acknowledges that Hepatitis B core proteins were known in art (Page 10). Moreover, Applicants' response of February 23, 2007, provides several references disclosing HBV antigens derived from surface and core proteins. These and other HBV antigens were known in the art at the time of the invention. For example, HBV core antigens were known to induce specific immune responses in chimpanzees and to protect the animals against HBV during challenge experiments (*See* Tabor et al. US Patent 4,547,367 filed on Dec. 20, 1983, e.g., Example 1). HBV antigenic peptides (fragments of HBV proteins) that induce specific immune responses were also known at the time of the invention (*See* Machida et al. US Patent 5,019,386 filed on Aug 29, 1998, e.g., Figures 1 and 3 and Examples 3-5). Other HBV antigens that were known include: HBV e-antigen, DNA polymerase, and x-antigen (Ferrari C et al., *The Journal of Immunology* Vol. 145, 3442-3449, November 15, 1990 and Trepo C, et al., *Gut*, 1993; 34; 20-25). Thus, HBV antigens are proteins and portions of proteins of HBV capable of inducing a specific immune response and such antigens and their ability to produce protective immune responses were well known to the skilled artisan at the time the application was filed.

The nature of the invention is a method of inducing a specific immune response to an HBV antigen (i.e., an antigen specific immune response). The term specific immune response is an art known term that refers to an immune response in a subject to an inducing antigen that is specific to the inducing antigen (*See* page 4, column 2, paragraph 2, *Cellular and Molecular Immunology*, Abbas AK, et al., Copyright 1991). Specific immune responses include humoral responses, in which antibodies recognizing the antigen are produced, and cell-mediated responses, in which lymphocytes having antigen-specific recognition capabilities are produced (See, page 5, column 2, paragraphs 2-4, *Cellular and Molecular Immunology*, Abbas AK, et al., Copyright 1991 and the instant specification, page 2, lines 19-20).

The state of the prior art at the time of the invention was such that HBV antigens capable of inducing specific immune responses were well known. Methods for detecting, cloning, and sequencing HBV genomic DNA were routine and available to the skilled artisan (*See*, for example, Yokosuka O, et al., *Gastroenterology*. 1991 Jan;100(1):175-81). Thus, it would have been well within the purview of the skilled artisan using the guideance provided in the specification to produce and/or obtain clones of genes and fragments of genes encoding HBV antigens for use in the claimed methods.

With regard to the level of predictability in the art, it is important to reiterate that it is the scope of the HBV antigen genus that is in question, and not the method for inducing an antigen specific immune response per se. Thus, this inquiry should be aimed at determining the predictability that a particular HBV antigen will induce an antigen specific immune response when expressed in a subject according to the claimed invention. Other aspects of the claimed invention are, according to the Examiner, enabled. As discussed herein, HBV antigens capable of inducing specific immune responses were well known. One of skill in the art would simply need to select an antigen of choice based on the publicly available information on HBV antigens. The corresponding gene encoding the HBV antigen can be cloned into an expression vector and expressed in a subject to produce an antigen specific immune response in view of the teachings in the instant specification.

Regarding the level of skill in the art, guided by the teachings of the instant specification, a person of ordinary skill would have been able to identify an appropriate HBV antigen and prepare an expression plasmid vector capable of expressing the antigen in a subject. The skilled artisan

would have also been capable of administering the expression plasmid vector according to the claimed method to induce an antigen specific immune response in a subject.

As the Examiner indicates, the specification is enabling for the claimed methods wherein the HBV antigen is a HBV surface antigen protein. Thus, to enable the full scope of the HBV antigen genus the specification need only provide sufficient direction to instruct the skilled artisan to identify HBV antigens other than surface antigens that induce specific immune responses and obtain and/or produce expression plasmid vectors encoding such antigens for use in the claimed methods. As discussed above, exemplary HBV antigens are disclosed in the specification. These and other HBV antigens were known in the art at time of the invention. Because genes encoding HBV non-surface antigens were known at the time of the invention, one would have only required knowledge of recombinant biology techniques, for which guidance is provided in the instant specification, to generate expression plasmid vectors that were capable of expression the antigens.

The specification also provides working examples that demonstrate induction of specific immune responses to HBV antigens. Examples of preparing expression plasmid vectors that express pre-S1, pre-S2, and S HBV antigens are provided (e.g., *See* Section 1.2 of Example 1 and Figures 1 - 5). In addition, the specification provides multiple examples in which mice (three different strains) and rabbits are administered expression plasmid vectors encoding the foregoing HBV antigens (e.g., *See* Examples 1-3, pages 11-23; Tables 1-5, pages 24-28; and Figures 6-10). These examples demonstrate that the HBV antigens are expressed in subjects, and that specific immune responses are induced against them. The examples also indicate that specific immune responses to HBV antigens administered according to the claimed methods can remain constant in subjects for more than 6 months and that type IgG antibodies are produced which are characteristic of a response that is T-cell dependent (e.g., See page 23).

The amount of experimentation needed for one of ordinary skill in the art to carry out the claimed methods is reasonable. Again, as indicated by the Examiner, the specification is enabling for the claimed methods wherein the HBV antigen is a HBV surface antigen protein. Thus, to carry out the methods with a non-surface antigen, the skilled artisan need only select a HBV non-surface antigen as disclosed in the specification and/or known in the art, obtain or prepare (using methods

well known in the art) an expression plasmid vector encoding the antigen, and carry out the administeration methods in a subject.

Applicants assert that the foregoing Wands analysis is properly focused on the issue at hand, which is to establish the scope of enablement for the claimed HBV antigen genus. Applicants assert that this analysis supports a determination that the disclosure does satisfy the enablement requirement for the methods as claimed, and that any necessary experimentation is not undue.

In the instant office action the Examiner has provided a series of remarks to the Applicant's response of February 23, 2007. Applicants address those remarks herein below.

The Examiner asserts that Babiuk et al. (2003) demonstrates considerable experimentation was needed to develop DNA vaccines and, therefore, amply demonstrates unpredictability in the art of DNA vaccination. Applicants respectfully disagree with these assertions. First, experimentation, even considerable experimentation (as the Examiner argues), is not indicative of unpredictability. In fact, a considerable amount of experimentation is permissible for enablement (MPEP 2164.06). Second, Babiuk discusses several approaches for improving the efficiency of DNA vaccine, but does not suggest that such vaccines are unpredictable. Babiuk clearly indicates that "DNA vaccination has many advantages over conventional vaccines" (page 649, column 1) and discusses several exemplary advantages. In one example, Babiuk indicates that an advantage of DNA vaccines is that they induce a more balanced Th1/Th2 like immune response (page 649, column 2). The teachings of Babiuk supports predictability in the art of DNA vaccines.

Rubyani et al. (2001) is cited by the Examiner for its teachings regarding technical hurdles hindering in vivo gene expression. Rubyani is a chapter on gene therapy giving "a brief overview of the success factors which are essential for clinical efficacy and safety" (See page 115, paragraph 2). The discussion of technical hurdles, which is pointed out by the Examiner, is within this context of clinical efficacy and safety (See Rubyani, page 123, section 3.3). Applicants remind the Examiner that issues such as optimization and safety of a therapeutic agent are to be properly left to the FDA, not the USPTO (See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA]."). Thus, the teachings of Rubyani are not relevant to determining the scope of enablement of the claimed invention.

Further, in order to rebut any teachings of the post filing Rubanyi et al. reference, Applicants present another post-filing reference Yang et al. Yang et al demonstrate in human subjects that DNA vaccination is not unpredictable and in fact results in T cell activation that is specific for HBV antigens (both envelope HBVs and core antigens) (Yang et al Gene Therapy (2006) 13: 1110-1117). Other references disclosing the effectiveness of DNA vaccination in other disease models in humans include: Catanzaro et al. Vaccine 2007, 25: 4085-4092 (HIV, intramuscular injection) and Martin et al. J. Infect. Dis 2007, 196: 1732-1740 (West Nile Virus).

In the Applicants' Response of February 23, 2007, Kuhober et al. (1996) is cited to support predictability of the claimed invention. In rebuttal, the Examiner argues that the results described in Kuhober do not demonstrate that immunization with a vector encoding HBV core antigen would be protective, or that the results presented for mice would be predictive of an immune response in other species. Applicants assert that Tabor (cited above) teaches that HBV core antigens induce a protective immune response in non-human primates. Thus, the administration of an expression plasmid vector that expresses a HBV core antigen according to the claimed methods is expected to induce a protective and specific immune response in multiple species including primates.

Regarding Haynes et al. (1996), which was cited by the Applicants, the Examiner argues that the reference does not provide evidence that the instant invention was enabled as of its filing date. The Examiner argues that the prior art generally acknowledges the critical role of the particular antigen used in DNA vaccination protocols, and asserts that Haynes confirms unpredictability of DNA vaccinations in large mammals (reciting excerpts from page 38, column 2, paragraph 2 of Haynes). However, the Examiner mischaracterizes the Haynes reference. The same section that the Examiner refers to (reproduced below) writes that several reports demonstrate that DNA vaccination elicits humoral, protective, and cytotoxic cellular immune responses. In fact, one of the reports (Davis HL et al. *Hum. Mol. Genet.* 1993; 2: 1847-1851) is the inventors' own work published after the filing date of the instant invention, which includes the experiments carried out according to the methods and teachings of the instant application.

> Following the above report, a number of other laboratories demonstrated the potential for eliciting antigen-specific immune responses in rodents and other animals following intramuscular or

> intradermal injection of varying amounts of plasmid DNA (Ulmer et al., 1993: Wang et al, 1993; Davis et al., 1993; Raz et al., 1994; Robinson et al., 1993; Cox et al., 1993; Sedegah et al., 1994). These studies were based on reported observations by Wolff and co-workers (Wolff et al., 1991, 1990) which demonstrated that direct muscle inoculation of plasmid DNA resulted in low level, sustained gene expression in rodent muscle for as much as 1 year following injection. Gene expression following muscle inoculation was also demonstrated in nonhuman primate muscle but at a significantly reduced efficiency (Jiao et al., 1992). The muscle injection DNA vaccine reports demonstrated conclusively that humoral, protective, and cytotoxic cellular immune responses could be elicited against a variety of antigens following this simple procedure.

The Examiner submits Ertl et al. (1996) in support of an argument for unpredictability in the art of DNA vaccinations. Applicants respectfully disagree. In fact, Ertl also cites work of the inventors (Davis HL et al. *Vaccine*. 1994 Dec;12(16):1503-9) to indicate that DNA vaccination produces "both a humoral and cell-mediated immunity" (*See* Ertl, page 2, paragraph 2) and that certain drugs causing muscle damage "improve the efficacy of genetic vaccines" (*See* Ertl, page 3, paragraph 2). Also citing the work of the inventors (Davis HL et al. *Hum. Mol. Genet.* 1993; 2: 1847-1851), Ertl indicates that compared with traditional vaccines, genetic vaccines "result in a longer lasting immune response". Thus, Ertl is consistent with the teachings of the invention regarding DNA vaccinations.

Based upon the foregoing, Applicant respectfully submits that the claimed invention is enabled. Accordingly, withdrawal of the rejection of claims 32-47 under 35 U.S.C. § 112 is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: July 22, 2008

Respectfully submitted,

By _____

Helen C. Lockhart
Registration No.: 39,248
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000